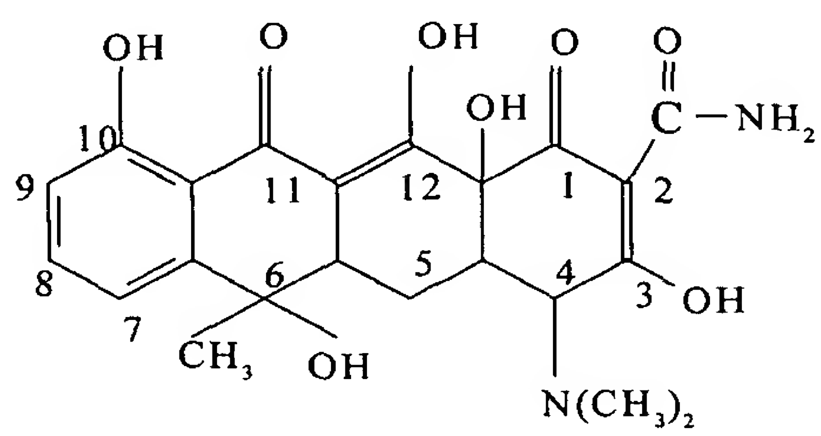
Please replace the paragraph b ginning on page 17, line 5, through page 18, line 8, with the following paragraph:

Tetracycline, which is well known to those of skill in the art, has the structure:



A2

It is intended herein for the term "tetracycline" to encompass all pharmaceutically active species of tetracycline compounds, solutions thereof and mixtures thereof, prodrugs thereof and any drug recognized as a tetracycline. Tetracycline includes forms, such as hydrated forms, and compositions such as aqueous solutions, hydrolyzed products or ionized products of these compounds; and these compounds may contain different numbers of attached water molecules. Thus, as used herein, the term tetracycline compound encompasses all derivatives and analogs and modified forms thereof, including but not limited to, those set forth herein. Tetracycline and tetracycline-like compounds include, but are not limited to aspirin, aureomycin, apicycline, chlortetracycline, clomocycline, demeclocyline, guamecycline, lymecycline, meclocycline, methacycline, minocycline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, and senociclin, as well as any others falling within the above formula. Also included among tetracycline-like compounds are compounds that alter bacterial folic acid metabolism, such as sulfa drugs, including sulfonamides, and thalidomide. Such compounds can be identified by their ability to alter bacterial folic acid metabolism.

Please replace the paragraph on page 20, lines 13-24, with the following paragraph:

Thus, reference, for example, to "IL-1" encompasses all proteins encoded by the IL-1 gene family including IL-1α, IL-1β, IL-1Ra and icIL-1Ra, or an equivalent molecule obtained from any other source or that has been prepared synthetically. It is intended to encompass IL-1 with conservative amino acid substitutions that do not substantially alter its activity. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. *Molecular Biology of the Gene*, 4th Edition, 1987, The Benjamin/Cummings Pub. co., p.224).

A3 cont.

Please replace the paragraph beginning on page 32, line 8, through page 33, line 2, with the following paragraph:

A4

For clarity of disclosure, and not by way of limitation, the detailed description is divided into the subsections that follow. The description below is exemplified by reference to viral hemorrhagic diseases. It is understood that the methods, compositions, combinations and kits provided and described herein may be used for treatment of any disorder, disease or condition characterized by a deleterious immune response, particularly, but not limited to, those specified herein. Such diseases, conditions and disorders include, but are not limited to: viral infections, such as viral hemorrhagic infections, lentivirus infections, HIV infections, herpes virus infections; bacterial infections, particularly infection with pathogenic strains of *E. coli* and *Streptococcus*; viruses associated with sleep disorders, such as HIV; parasitic infections, such as malaria; autoimmune diseases, such as thyroid diseases, rheumatoid arthritis, and lupus; sepsis; cachexia, such as the wasting associated with HIV infection and cancer; rheumatoid arthritis; chronic myelogenous leukemia and transplanted bone marrow-induced graft-versus-host disease; septic shock; immune complex-induced colitis; cerebrospinal fluid inflammation; endotoxemia; autoimmune disorders; multiple sclerosis; cell death associated with apoptosis; thyroid diseases and other endocrine disorders in which TNF or IL-1 is implicated or is a mediator; gynecological disorders, including endometriosis and infections associated therewith; and other diseases mediated by or associated with IL-1 and/or TNF. It is also understood that IL-1 and TNF expression serve as markers for these disorders to monitor the treatments herein and

A4 cont.

the blood compositions herein, but that these inflammatory response compounds are not necessarily the only agents involved.

Please replace the paragraph on page 36, lines 1-7, with the following paragraph:

A5

For purposes herein a tetracycline is any compound recognized by those of skill in the art to have the anti-inflammatory activities of a tetracycline and includes, all derivatives, including salts, esters and acids, analogs, prodrugs, modified forms thereof, and other compounds related to tetracycline as described above. The following are exemplary tetracycline compounds intended for use in the methods and compositions and combinations provided herein.

~~Please replace~~ the paragraph beginning on page 41, line 27, through page 42, line 13, with the following paragraph:

A6

(8) Other Chemically-Modified Tetracyclines

Other tetracyclines include, but are not limited to, dedimethylaminotetracyclines, which include 4-dedimethylaminotetracycline, 4-dedimethylamino-5-oxytetracycline, 4-dedimethylamino-7-chlortetracycline, 4-hydroxy-4-dedimethylaminotetracycline, 5a, 6-anhydro-4-hydroxy-4-dedimethylaminotetracycline, 6*α*-deoxy-5-hydroxy-4-dedimethyl-aminotetracycline, 6-demethyl-6-deoxy-4-dedimethylaminotetracycline, 4-dedimethyl-amino-12a-deoxytetracycline, 4-dedimethylamino-11-hydroxy-12a-deoxytetracycline, 12a-deoxy-4-deoxy-4-dedimethylaminotetracycline, 6*α*-deoxy-5-hydroxy-4-dedimethyl-aminodoxycycline, 12a,4a-anhydro-4-dedimethylaminotetracycline and minocycline-CMT *i.e.*, 7-dimethylamino-6-demethyl-6-deoxy-4-dedimethylaminotetracycline. Further examples of chemically-modified tetracyclines contemplated for use herein, include but are not limited to, 6a-benzylthiomethylenetetracycline, the 2-nitrilo analogs of tetracycline (tetracyclinonitrile), the mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, 11a-chlortetracycline, tetracycline pyrazole and 12a-deoxytetracycline and its derivatives (see, *e.g.*, U.S. Patent No. 5,532,227).

Please replace the paragraph on page 49, lines 5-12, with the following paragraph:

A7

Monoclonal antibodies, particularly humanized antibodies can be used. Anti-IL-1 antibodies are known (see, *e.g.*, U.S. Patent Nos. 4,772,685 and 4,994,553). Anti-IL-1 receptor antibodies are also known (see, *e.g.*, Chen et al., *Cancer Res.*, 58(16):

A7 cont.

3668-76 (1998); Clark et al., *J. Interferon Cytokine Res.*, 16(12): 1079-88 (1996); Zerek-Melen et al., *Eur. J. Endocrinol.*, 131(5): 531-4 (1994); McIntyre *et al.* (1991) *J. Exp. Med.*, 173(4):931-9; Benjamin *et al.* (1990) *Prog. Clin. Biol. Res.*, 349:355-6).

Please replace the paragraph on page 53, lines 4-21, with the following paragraph:

A8

The TNF receptor antagonist can be a TNF receptor death domain ligand protein, a tumor necrosis factor binding protein (TNF-BP), a TNF receptor-IgG heavy chain chimeric protein (Peppel et al., *J. Exp. Med.*, 174(6):1483-9 (1991)), a bacterial lipopolysaccharide binding peptide derived from CAP37 protein (U.S. Patent No. 5,877,151) and a Myxoma virus T2 protein (Schreiber et al., *J. Biol. Chem.*, 271(23):13333-41 (1996)). Exemplary TNF receptor death domain ligand proteins include those described in U.S. Patent Nos. 5,849,501, 5,847,099, 5,843,675, 5,852,173 and 5,712,381 (see, also SEQ ID Nos. 18, 19, 20 and 21). Also, the TNF-BPs described in U.S. Patent No. 5,811,261, which describes TBP-1, a 180 amino acid protein isolated from human urine, U.S. Patent Nos. 5,808,029, 5,776,895 and 5,750,503, which describe chimeric TNF-BPs containing the soluble portion of the P55 TNF receptor and all but the first domain of the constant region of IgG1 or IgG3 heavy chains, and the TNF-BPs described in Colagiovanni et al., *Immunopharmacol. Immunotoxicol.*, 18(3):397-419 (1996) and Olsson et al., *Biotherapy.*, 3(2):159-65 (1991), which describes a 50 kDa protein isolated from human urine, can be the TNF receptor antagonist.

Please replace the paragraph on page 56, lines 1-23, with the following paragraph:

A9

(c) Anti-Flaviviridae Vaccine

An anti-Flaviviridae vaccine, such as an anti-Dengue virus vaccine, can be used (*e.g.*, U.S. Patent No. 5,494,671, Becker, *Virus Genes*, 9(1):33-45 (1994) (Dengue fever virus and Japanese encephalitis virus synthetic peptides with motifs to fit HLA class I haplotypes), Blok, et al., *Virology.*, 187(2):573-90 (1992) (Dengue-2 virus vaccine), Dharakul, et al., *J. Infect. Dis.*, 170(1):27-33 (1994) (live attenuated Dengue virus type 2 vaccine), Green, et al., *J Virol.*, 67(10):5962-7 (1993) (live attenuated Dengue virus type 1 vaccine), Hoke, et al., *Am. J. Trop. Med. Hyg.*, 43(2):219-26 (1990) (attenuated Dengue 4 (341750 Carib) virus vaccine), Khin, et al., *Am. J. Trop.*

Med. Hyg., 51(6):864-9 (1994), (Dengue-2 PDK53 candidate vaccine), Kinney, et al., *Virology.*, 230(2):300-8 (1997) (attenuated vaccine derivative, strain PDK-53), Leblois, et al., *Nucleic Acids Res.*, 21(7):1668 (1993) (Dengue virus type 2 (strain PR-159) NS1 gene and its vaccine derivative), Marchette, et al., *Am. J. Trop. Med. Hyg.*, 43(2):212-8 (1990) (attenuated Dengue 4 (341750 Carib) virus vaccine), Price, et al., *Am. J. Epidemiol.*, 94(6):598-607 (1971) (injection with Dengue virus), Putnak, et al., *Am. J. Trop. Med. Hyg.*, 55(5):504-10 (1996) (purified, inactivated, Dengue-2 virus vaccine prototype made in fetal rhesus lung cells), Putnak, et al., *J. Infect. Dis.*, 174(6):1176-84 (1996) (purified, inactivated, Dengue-2 virus vaccine prototype in Vero cells), Schlesinger, et al., *J Gen Virol.*, 68(3):853-7 (1987) (Dengue 2 virus non-structural glycoprotein NS1)).

A9 cont

Please replace the paragraph on page 58, lines 18-27, with the following paragraph:

A10

An anti-Marburg antibody can be used. The antibodies can be raised against Marburg virus protein sequences with the following Genbank accession numbers: AAC40455-AAC40460, VHIWMV, RRIWMV, S44052-S44053, S33316, S32582-S32583, A45705, B45705, S44049, S44054, CAA78114-CAA78120, CAA82536-CAA82542, CAA45746-CAA45749, CAA48507-CAA48509 and AAA46562-AAA46563 or encoded by nucleic acid molecules containing nucleotide sequences with the following Genbank accession numbers: AF005730-AF005735, Z12132, Z29337, X64405-X64406, X68493-X68495, M72714, M92834 and M36065.

Please replace the paragraph on page 59, lines 11-14, with the following paragraph:

A11

(d) Anti-Arenaviridae Antibody

An anti-Arenaviridae antibody, such as an anti-Junin virus antibody, can be used (see, *e.g.*, the antibodies described in Mackenzie, et al., *Am. J. Trop. Med. Hyg.*, 14(6):1079-84 (1965)).

Please replace the paragraph on page 81, lines 7-23, with the following paragraph:

A12

U.S. Patent No. 4,154,819 describes a process for preparing a γ-globulin solution suitable for the intravenous application by treating the solution of γ-globulin with acetimido ethyl ester hydrochloride, diketene, formimido ethyl ester hydrochloride

or propanesulfone at a pH of about 9, thereafter adjusting the pH to about 7 to 7.5, and separating the solution from the solids by dialysis or fractionation followed by sterile filtration. Generally, the diketene is employed in about 0.02 g per g of protein in the γ-globulin solution.

U.S. Patent No. 4,374,763 describes a process for producing γ-globulin suitable for use in intravenous administration and of an anticomplementary activity of lower than 20% by bringing Cohn's Fraction II for the gamma-globulin into suspension in an aqueous solution of a monosaccharide, disaccharide or sugar alcohol, adjusting the pH of the suspension to about 7.0 to 9.0, adding dextran of an average molecular weight of 10,000 to 70,000 into the suspension to produce an aqueous about 2 to 10% (w/v) solution of dextran, and after removing the thus formed precipitate, adding ammonium sulfate to the mother liquor to precipitate the gamma-globulin.

A12 CONT.

Please replace the paragraph beginning on page 93, line 20, through page 94, line 2, with the following paragraph:

c. Methods of treatment using the resulting blood-derived compositions

The compositions thus produced are suitable for treating viral hemorrhagic diseases or disorders or other diseases, disorders or syndromes involving such cytotoxic responses including, but not limited to, other acute infectious diseases, sepsis, cachexia, rheumatoid arthritis and other autoimmune disorders, acute cardiovascular events, chronic myelogenous leukemia and transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis. Accordingly, methods for treating or preventing a viral hemorrhagic disease or disorder or other such disorders involving such cytotoxic responses in a mammal are provided. These methods include the steps of administering to the mammal an effective amount of the immune composition(s) produced according to the above processes.

A13

Please replace the paragraph beginning on page 99, line 12, through page 100, line 3, with the following paragraph:

Filoviruses are enveloped, nonsegmented negative-stranded RNA viruses. The two species, Marburg and Ebola virus, are serologically, biochemically, and genetically distinct. Classification, virion morphology and structure, genomic organization and diagnosis are described in detail in Beer et al., *Naturwissenschaften*, 86:8-17 (1999),

A14

A14 cont.

Springer-Verlag 1999. Marburg and Ebola viruses are pleomorphic particles that vary greatly in length, but the unit length associated with peak infectivity is 790 nm for Marburg virus and 970 nm for Ebola virus (Regnery et al., *J. Virol.*, 36:465-469 (1980)). The virions appear as either long filamentous (and sometimes branched) forms or in shorter U-shaped, 6-shaped (mace-shaped), or circular (ring) configurations (Murphy et al., Paltyn S.R. (ed) Ebola virus hemorrhagic fever, Elsevier/North-Holland, Amsterdam, pp. 61-82 (1978); Peters et al., Martini and Siegert (eds) Marburg virus disease, Springer, Berlin Heidelberg, New York, pp. 68-83 (1971)). Virions have a uniform diameter of 80 nm and a density of 1.14 g/ml. They are composed of a helical nucleocapsid, a closely apposed envelope derived from the host cell plasma membrane, and a surface projection layer composed of trimers of viral glycoprotein (GP) (Feldmann *et al.* (1991) *Virology 182*:353-356). All filoviruses contain one molecule of noninfectious, linear, negative-sense, single-stranded RNA with a M_r of 4.2 x 10^6, constituting 1.1% of the virion mass (Kiley M.P *et al.* (1988) *J. Gen. Virol. 69*:1957-1567 (1988); Regnery *et al.* (1980) *J. Virol. 36*:465-469).

Please replace the paragraph beginning on page 103, line 27, through page 104, line 12, with the following paragraph:

A15

The viral genome of approximately 11 kb is infectious, has a messenger-like positive polarity, and can be translated *in vitro*. The 5′ end of the RNA has a type I cap structure but lacks a poly A tail at the 3′ end (Rice et al., *Science*, 229:726-33 (1985); Hahnet al., *Virology*, 162:167-80 (1988); Irie et al., *Gene*, 74:197-211 (1989)). It contains a single open reading frame of about 10,000 nucleotides encoding three structural and seven nonstructural proteins. The gene order is 5′-C-prM(M)-E-NSI-NS2A-NS2B-NS3-NS4A-NS4B-NS5. The proteins are synthesized as a polyprotein of about 3000 amino acids that is processed cotranslationally and posttranslationally by viral and host proteases (Biedrzycka et al., *J. Gen. Virol.*, 1987, 68:1317-26; Mackow et al., *J. Gen. Virol.*, 1987, 69:23-4; Speight et al., Virology, 1987, 159(2):217-28; Chambers et al., *Virology*, 1989, 169:100-9; Markoff et al., *J. Virol.*, 1989, 63:3345-52; Preugschar et al., *J. Virol.*, 1990, 64:4364-74; Falgout et al., *J. Virol.*, 1991, 65:2467-75; Preugschat et al., *J. Virol.*, 1991, 65:4749-58; Preugschat F., et al., *Virology*, 1991, 185:689-97; Cahour et al., *J. Virol.*, 1992, 66:1535-42).

Please replace the paragraph on page 107, lines 19-31, with the following paragraph:

Arenaviridae virus infection, and particularly Lassa virus, Machupo virus, or Pichinde virus infection, can be diagnosed by any methods known in the art according to clinical, immunological or molecular criteria. Any known immunological methods can be used in the diagnosis of Arenaviridae virus infection, and particularly Lassa virus, Machupo virus, or Pichinde virus infection (*see* Current Protocols in Immunology (Ed. Coligan et al.) John Wiley & Sons, Inc., 1997). Antibody-based or antigen-based immunological methods, including immuniprecipitation, Western blotting, dot blotting and *in situ* immuno-detection methods such as immunofluorescence, can be used. In a specific embodiment, anti-Arenaviridae virus or anti-Lassa virus, anti-Machupo virus and anti-Pichinde virus antibodies known to those of skill art in the or described herein can be used in the immunodiagnosis.

A16

Please replace the paragraph beginning on page 115, line 27, through page 116, line 5, with the following paragraph:

Group 5

The animals from this group were given, intravenously daily from the second day after infection until the sixth day, 0.3 ml of the serum collected from the animals of the group 1 on the first day after those animals were treated with doxycycline. In this volume, the Serum collected from the animals of group 1 contained 6.6 pg IL-1, 60 pg IL-1ra, 1.5 pg TNF and 25 pg sTNFr. The virus detection was provided by PCR-method on the second day after infection. From the first day after infection, the sera were taken from the mice of group 5 to detect concentration of IL-1, TNF, IL-1RA and sTNFr (Table 11).

A17

Please replace the paragraphs on page 129, lines 14-27, with the following paragraphs:

Group B2- 30 mice - was used for obtaining blood samples on day (0) and days 1, 3, 5, 6 and 12 post infection. Blood samples were obtained from the orbital sinuses (at every time point 3 mice were used for harvesting blood). All blood samples (500 μl each) were frozen at -70° C. After completion of the experiment, the concentrations of TNF-α, and IL-1β were measured.

A18

Groups C

Group C1 - control for mortality. 10 mice.

Group C2 - 26 mice - was used for obtaining blood samples on day (0) and days 1, 3, 5 and 12 post infection. Blood samples were obtained from the orbital sinuses (at every time point 3 mice were used for harvesting blood). All blood samples (500 μl) were frozen at -70° C. After completion of the experiment, the concentrations of TNF - α and IL-1β were measured.

a18 cont.

Please replace the paragraph on page 133, lines 4-25, with the following paragraph:

a19

Experimental Scheme

All animals were divided into groups, each contained 6 animals.

The guinea pigs were infected by the 5 LD_{50} of the Marburg virus.

Animals of the group A were used only for the virus control.

Animals of the group B after infection were treated by the human serum (SERUM1) with IgG against Marburg (titer IgG in ELISA 1:80), without IgG against Ebola and sTNFrI (950 pg/ml), TNFα (7.8 pg/ml), IL-1RA (136 pg/ml), IL-1β (3 pg/ml). Animals of the group B were given SERUM1 intracardially from day 3 after virus infection until day 14, every day at the following doses:

3 day - 200μl
4 day - 200μl
5 day - 400μl
6 day - 400μl
7 day - 600μl
8 day - 600μl
9 day - 600μl
10 day - 800μl
11 day - 800μl
12 day - 800μl
13 day - 800μl
14 day - 800μl.

Please replace the paragraph beginning on page 133, line 30, through page 134, line 5, with the following paragraph:

a20

Animals of the group C were given Serum 2 intracardially from day 3 after virus infecting until day 12, every day, at the following doses:

3 day - 200μl
4 day - 200μl
5 day - 400μl

a20 cont.

6 day - 400μl
7 day - 600μl
8 day - 600μl
9 day - 600μl
10 day - 800μl
11 day - 800μl
12 day - 800μl.

Please replace the paragraphs on page 134, lines 10-37, with the following paragraphs:

a21

Animals of group D were given Serum 3 intracardially from 3 day after virus infecting until day 12, every day, at the following doses:

3 day - 200μl
4 day - 200μl
5 day - 400μl
6 day - 400μl
7 day - 600μl
8 day - 600μl
9 day - 600μl
10 day - 800μl
11 day - 800μl
12 day - 800μl.

Animals of the group E were treated with human serum without the antibodies against Marburg and Ebola viruses, and the concentrations of TNF α-7.0 pg/ml, sTNFrI-20pg/ml, IL-1β-3 pg/ml, IL-1RA-20 pg/ml (SERUM 4). Animals of the group E were given Serum 4 intracardially from 3 days after virus, injecting every day, until day 12, at the following doses:

3 day - 200μl
4 day - 200μl
5 day - 400μl
6 day - 400μl
7 day - 600μl
8 day - 600μl
9 day - 600μl
10 day - 800μl
11 day - 800μl
12 day - 800μl.

Please replace the paragraph on page 144, lines 5-11, with the following paragraph:

a22

2. Plasma (citrated) is collected from these mice at 24 hr postinjection. One 0.2 ml sample of plasma from each mouse is set aside for testing for the presence of